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Chronic Inflammatory Demyelinating Polyneuropathy in Non-Hodgkin's Lymphoma

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A 42-year-old man was diagnosed with large cell non-Hodgkin's lymphoma 3 years after autologous bone marrow transplantation for Hodgkin's disease. The day before beginning systemic chemotherapy, the patient began to have symptoms of a sensorimotor neuropathy characterized by proximal and distal weakness, lower-extremity areflexia, elevated cerebrospinal fluid protein level, and evidence of demyelination on nerve conduction studies. Symptoms progressed despite two courses of intrathecal methotrexate, for possible lymphomatous meningitis, as well as systemic chemotherapy. The diagnosis of chronic inflammatory demyelinating polyneuropathy was made. Daily plasma exchange was performed for a total of 10 treatments with immediate improvement and eventual complete recovery in strength, sensation, and gait.

A review of the literature confirms that inflammatory demyelinating polyneuropathy is a highly unusual but important cause of peripheral nervous system dysfunction. The potential for complete response to plasma exchange should be recognized in patients with symptoms, signs, and nerve conduction studies suggestive of chronic inflammatory demyelinating polyneuropathy. Am. J. Hematol. 54:332–334, 1997.

Key words: non-Hodgkin's lymphoma; Guillain-Barré syndrome; demyelinating polyneuropathy; paraneoplastic syndromes; plasma exchange

CASE PRESENTATION

A 42-year-old man presented with acute weakness, leg pain, and difficulty walking 4 weeks after being diagnosed with large cell lymphoma. The patient was first diagnosed at age 28 with stage IIIB Hodgkin's disease. He went into complete remission after six cycles of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP). One year later he relapsed and was treated with MOPP alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for eight cycles followed by mantle-field radiation using attenuated doses.

Hodgkin's disease recurred in the peribiliary lymph nodes $8\frac{1}{2}$ years after the initial diagnosis. After one cycle of MOPP, one cycle of ABVD, and one cycle of dexamethasone, cisplatin, and cytosine arabinoside (DHAP), he underwent autologous bone marrow transplantation. The conditioning regimen comprised BCNU, etoposide, cytosine arabinoside, and cyclophosphamide (BEAC). After transplantation he received 30 Gy of involved-field radiation.

Three years after transplantation, he presented with crampy abdominal pain. Computed tomography (CT) scans demonstrated a cecal mass and axillary, iliac, inguinal, and mesenteric adenopathy. There was no mediastinal disease. He underwent right hemicolectomy for removal of a 4-cm mass; pathology revealed diffuse large cell lymphoma.

Four weeks after surgery, he complained of gait instability, but no neurologic abnormalities were detected. Chemotherapy was started using cyclophosphamide 750 mg/m^2 iv × 1, mitoxantrone 10 mg/m^2 iv × 1, vincristine 1 mg/m^2 iv × 1, and prednisone 100 mg po every day for 5 days (CNOP). Seven days after initiation of treatment, he presented with acute gait disturbance and crampy pain

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in the calves. Bilateral weakness of knee flexion, ankle dorsiflexion, plantar flexion, and extensor hallicus longis was present, and the patient's gait evidenced bilateral footdrop. He was unable to hop or toe walk. Muscle bulk was normal. The lower extremities were areflexic, and only right biceps and left triceps reflexes were elicited. Sensory loss was present; there was decreased vibratory sense below the knees and proprioceptive impairment at the ankles and toes. Pain sensation was preserved. Romberg sign was positive.

Cerebrospinal fluid (CSF) was clear with a protein level of 150 mg/dl. No abnormal cells were seen in the CSF. Magnetic resonance imaging (MRI) of the spinal cord demonstrated slight enhancement of the cauda equina. MRI of the head was normal. Nerve conduction studies were consistent with a primarily demyelinating polyneuropathy with conduction block and temporal dispersion in the tibial nerves bilaterally around the fibular head. No other conduction block was noted.

The patient's weakness plateaued over the following 2 weeks, and nerve conduction studies remained consistent with demyelination. Repeat CSF evaluation was unchanged. The patient was treated with intrathecal methotrexate 12 mg and hydrocortisone 25 mg for possible lymphomatous meningitis 25 days after the first cycle of chemotherapy was given. He received a second course of systemic chemotherapy, consisting of cyclophosphamide, mitoxantrone, and prednisone. Vincristine was withheld. Twelve days later, his symptoms were unchanged. He was given a second dose of intrathecal methotrexate and hydrocortisone.

Two weeks later, he had progression of the neurologic symptoms and, in addition, had parasthesias in the right hand. His gait was unsteady, and he had difficulty walking on his heels and toes and was unable to hop or tandem walk. The Romberg test was more abnormal. In addition to the previous pattern of weakness, there was now weakness of the biceps, triceps, and hip flexors. He had a marked sustention tremor. The sensory examination was notable for reduced vibration sensation to the patella on the left and to the anterior superior iliac spine on the right. Proprioception was absent at the toes and poor at the knees. Spinothalamic function was preserved. Reflexes were absent. Nerve conduction studies showed worsening nerve conduction velocity of the tibial nerves.

Seven weeks after his admission for acute leg weakness, daily plasma exchange was started and continued for 10 days. Marked improvement in the weakness and proprioceptive abnormalities occurred after the first plasma exchange treatment. Three weeks after completion of plasma exchange, he was able to squat, hop, and heel and toe walk. Position sense was normal. Vibratory sense was still markedly decreased in the feet and slightly decreased in the knees and hips. He continued to be areflexic. The hand tremor persisted.

The patient was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). Seven weeks after the completion of plasma exchange, power remained normal. Vibration sensation had not improved. Reflexes in the biceps, triceps, brachioradialis, and knees were elicited with reinforcement.

He completed eight cycles of therapy with cyclophosphamide, mitoxantrone, and prednisone without further difficulty. He remains in complete clinical remission 11 months after completion of chemotherapy and 18 months after diagnosis. The neurologic examination is entirely normal.

DISCUSSION

Symptomatic disorders of the peripheral nervous system occur in only 5–8% of patients with lymphoma [1–4]. Infection with herpesviruses, neurotoxicity induced by vincristine, and direct involvement by lymphoma are the most common causes of peripheral nervous system abnormalities in patients with lymphoma [2]. Brachial neuritis has also occurred in several patients with Hodgkin's disease [3,5,6].

Guillain-Barré syndrome, also called acute inflammatory demyelinating polyneuropathy (AIDP), occurs in Hodgkin's disease [1,7–9]. Additionally, several recent reports describe acute and subacute IDP in patients undergoing autologous or allogeneic bone marrow transplantation for non-Hodgkin's lymphoma or chronic myelogenous leukemia (CML). One 40-year-old man with non-Hodgkin's lymphoma developed AIDP 7 days after infusion of autologous marrow. The patient responded to high-dose corticosteroids after an unsuccessful trial of plasma exchange [10]. A 19-year-old man with CML developed AIDP complicated by respiratory failure several days after infusion of allogeneic marrow. The patient was treated with supportive measures and had persistent weakness and pedal paresthesias 1 year after transplantation [11]. Another patient undergoing allogeneic transplantation for CML developed acute inflammatory demyelinating polyradiculitis 100 days after transplantation. This patient had some improvement with plasma exchange and more rapid recovery once cyclosporine was discontinued but continued to have residual paresis [12]. Two bone marrow transplant patients with underlying CIDP, one undergoing allogeneic transplantation for CML and the other undergoing autologous transplantation for Hodgkin's disease, had exacerbation of the neurologic disorder in the acute transplantation period. Both patients developed quadriplegia that did not respond to steroids, plasma exchange, or immunoglobulin, all standard treatment for CIDP [13], and both patients died within 200 days of transplantation [14].

The findings and clinical course in our patient are most consistent with a diagnosis of CIDP. Symptoms began 4

weeks after a diagnosis of non-Hodgkin's lymphoma and 1 day before his first cycle of chemotherapy. Weakness and paresthesias progressed over 8 weeks despite high-dose oral corticosteroids (given as part of his chemotherapy) and intrathecal methotrexate. He has had sustained recovery after only one course of intensive plasma exchange.

The clinical features in this patient that support the diagnosis of CIDP and help distinguish it from Guillain-Barré include the prolonged clinical course, the severity of the sensory abnormalities, and the nerve conduction slowing at presentation [15,16]. Although conduction block around the fibular head is a not uncommon area for focal block and slowing due to other conditions such as compression, the patient's nerve conduction studies were consistent overall with demyelination. Typical Guillain-Barré syndrome is associated predominantly with motor weakness that peaks at 4 weeks into the illness, with mild sensory symptoms or signs, and with nerve conduction abnormalities only in the advanced stages of the illness [16]. In addition, spinal MRI in this patient demonstrated enhancement of the cauda equina, a finding previously described in patients with CIDP [17]. It is possible that the patient had an atypical form of Guillain-Barré that improved coincidentally with plasma exchange.

The pathogenesis of AIDP and CIDP in patients with lymphoma or patients undergoing bone marrow transplantation is unclear. It has been suggested that immunosuppression, either therapeutic [18] or associated with lymphoma and its treatment [9], may paradoxically allow for the development of autoantibodies against the peripheral nervous system.

This case of CIDP not related to high-dose chemotherapy in non-Hodgkin's lymphoma illustrates the major morbidity of CIDP in the lymphoma patient and the potential for complete recovery with plasma exchange.

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